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http://dx.doi.org/10.1016/j.jacc.2013.04.077

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Reply

All Vasodilators Are Not Equal

We appreciate the commentary by Ms. Nel and Greaves regarding our study (1). Previous studies have demonstrated that dipyridamole, regadenoson, and adenosine all achieve maximal coronary hyperemic flow via endothelial-independent vasodilation of the microvasculature (2–4). Although dobutamine stress has a different mechanism of action, the resulting hyperemia is similar in magnitude to adenosine (5). More important, in both the larger cohort from which this study was derived (6) and in other large cohorts (7), the stressor used was not informative to the multivariable model for predicting cardiac events. Accordingly, we do not believe that the use of multiple stress agents is likely to have resulted in a type 1 error or a false-positive association between CFR and outcomes.

In response to concerns raised by Nel and Greaves regarding incorporation bias, this problem occurs in diagnostic studies in which the test being evaluated is available to referring clinicians, and thus, may influence the diagnostic endpoint. In our study of prognosis, CFR was not available to referring clinicians, and consequently, could not have influenced clinical decision making. Furthermore, the clinical endpoints were adjudicated blinded to CFR values. Finally, for inclusion in this study, normal PET myocardial perfusion imaging was defined not on the basis of CFR, but rather on semiquantitative interpretation of myocardial perfusion scans.

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http://dx.doi.org/10.1016/j.jacc.2013.05.037

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A Randomized Comparison of Pulmonary Vein Isolation With Versus Without Concomitant Renal Artery Denervation in Patients With Refractory Symptomatic Atrial Fibrillation and Resistant Hypertension

With the advent of renal artery denervation, numerous publications have been forthcoming. Previously, we petitioned the *Journal* as well as other publications about the lack of citation of our earlier studies (1–6) using intravascular electrode catheters to ablate autonomic nerves on the outside of blood vessels. We can appreciate the reluctance of the *Journal* to include these citations at that time based on the difference between the intravascular ablation of nerves in the renal arteries affecting blood pressure (7,8) rather than intravascular ablation of nerves outside of blood vessels affecting heart rate and cardiac arrhythmias (9). However, recent reports have documented the consistent and independent effects of renal sympathetic denervation (RSD) on heart rate reduction (10,11). More conclusive evidence supporting our contention is based on the experimental studies of Zhao et al. (12) and the recent clinical study by Pokushalov et al. (13), which have shown that RSD can be used to reduce the

incidence of atrial fibrillation. Although the exact mechanisms are still unclear, it has been suggested that ablation of afferent nerves arising from the renal arteries, or other arteries for that matter, can reduce central sympathetic outflow back to the renal nerves as well as via cardiac nerves to the heart, thereby affecting blood pressure (14) as well as heart rate and cardiac arrhythmias (15). Therefore, we are again requesting the *Journal* to consider including citations of our previous work in future reports dealing with intravascular RSD for resistant hypertension and other collateral benefits.

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http://dx.doi.org/10.1016/j.jacc.2013.05.068

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